PCT/EP03/05988

What is claimed is:

Replaced by Certicle 3 4

1. A combination which comprises (a) a HER-1 or a HER-2 antibody or (b) at least one antineoplastic agent selected from the group consisting of aromatase inhibitors antiestrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, protein kinase C inhibitors, anti-angiogenic compounds, gonadorelin agonists, anti-androgens, histone deacetylase inhibitors, and S-adenosylmethionine decarboxylase inhibitors and (c) an epothilone derivative of formula I

$$\begin{array}{c|c}
R & Z \\
\downarrow & \downarrow & \downarrow \\
HO & \downarrow & \downarrow \\
O & OH & O
\end{array}$$

$$\begin{array}{c}
S \\
N \\
\end{array}$$

$$(I)$$

wherein A represents O or NR_N , wherein R_N is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino, aminomethyl or methylthio, and Z is O or a bond, in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

- 2. A combination which comprises
 - (a) a HER-1 or a HER-2 antibody and
 - (b) an epothilone derivative of formula I

$$\begin{array}{c|c}
R & Z \\
\hline
 & S \\
\hline
 & N \\
\hline
 & O \\
 & O \\
\hline
 & O \\
 & O \\
\hline
 & O \\
 & O \\
\hline
 & O \\
 & O \\
\hline
 & O \\
 & O \\
\hline
 & O \\
 & O \\
\hline
 & O \\
 & O \\
\hline
 & O \\
\hline
 & O \\
\hline
 & O \\
\hline
 & O \\$$

wherein A represents O or NR_N , wherein R_N is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl and Z is O or a bond,

in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

3. A combination which comprises (a) at least one antineoplastic agent selected from the group consisting of topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, protein kinase C inhibitors, anti-angiogenic compounds, gonadorelin agonists, anti-androgens, histone deacetylase inhibitors, and S-adenosylmethionine decarboxylase inhibitors and (b) an epothilone derivative of formula I

wherein A represents O or NR_N , wherein R_N is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino, aminomethyl or methylthio, and Z is O or a bond,

in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

4. A combination which comprises (a) at least one antineoplastic agent selected from the group consisting of aromatase inhibitors and antiestrogens and (b) an epothilone derivative of formula I

wherein A represents O or NR_N , wherein R_N is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino, aminomethyl or methylthio, and Z is O or a bond,

in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

- 5. Combination according to claim 1 which comprises (a) a HER-1 or a HER-2 antibody or (b) at least one antineoplastic agent selected from the group consisting of aromatase inhibitors antiestrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, protein kinase C inhibitors, anti-angiogenic compounds, gonadorelin agonists, anti-androgens, histone deacetylase inhibitors, and S-adenosylmethionine decarboxylase inhibitors and (c) an epothilone derivative of formula I wherein A represents O or NR_N, wherein R_N is hydrogen or lower alkyl, R' is methyl or methylthio, R is hydrogen or lower alkyl, and Z is O or a bond, in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.
- 6. Combination according to claim 1,2 or 5 wherein the HER-1 or HER-2 antibody is trastuzumab.
- 7. Combination according to claim 1, 3 or 5 wherein the antineoplastic agent is a topolsomerase I inhibitor.
- Combination according to claim 1, 3 or 5 wherein the antineoplastic agent is a topoisomerase II inhibitor.

- 9. Combination according to claim 1, 4 or 5 wherein the antineoplastic agent is an aromatase inhibitor.
- 10. Combination according to claim 1, 3 or 5 wherein the antineoplastic agent is a microtubule active agent.
- 11. Combination according to claim 1 to 10 wherein the epothilone derivative is epothilone B.
- 12. Combination according to any one of claims 1 to 11 which is a combined preparation
- 13. Method of treating a warm-blooded animal having a proliferative disease comprising administering to the animal a combination according to any one of claims 1 to 9 in a quantity which is jointly therapeutically effective against a proliferative disease and in which the compounds can also be present in the form of their pharmaceutically acceptable salts.
- 14. A pharmaceutical composition comprising a quantity which is jointly therapeutically effective against a proliferative disease of a combination according to any one of claims 1 to 12 and at least one pharmaceutically acceptable carrier.
- 15. A combination according to any one of claims 1 to 12 for use in the treatment of a proliferative disease.
- 16. Use of a combination according to any one of claims 1 to 12 for the preparation of a medicament for the treatment of a proliferative disease.
- 17. Use according to claim 15 or 16 wherein the proliferative disease is a solid tumor disease.
- 18. Use of (a) a HER-1 or a HER-2 antibody or (b) at least one antineoplastic agent selected from the group consisting of aromatase inhibitors antiestrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, protein kinase C inhibitors, anti-angiogenic compounds, gonadorelin agonists, anti-androgens, histone

deacetylase inhibitors, and S-adenosylmethionine decarboxylase inhibitors in combination with (c) an epothilone derivative of formula I

wherein A represents O or NR_N , wherein R_N is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino, aminomethyl or methylthio, and Z is O or a bond,

for the preparation of a medicament for the treatment of a proliferative disease.

19. A commercial package comprising (a) a HER-1 or a HER-2 antibody or (b) at least one antineoplastic agent selected from the group consisting of aromatase inhibitors antiestrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, protein kinase C inhibitors, anti-angiogenic compounds, gonadorelin agonists, anti-androgens, histone deacetylase inhibitors, and S-adenosylmethionine decarboxylase inhibitors and (c) an epothilone derivative of formula I

wherein A represents O or NR_N , wherein R_N is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino, aminomethyl or methylthio, and Z is O or a bond,

together with instructions for simultaneous, separate or sequential use thereof in the treatment of a proliferative disease.